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Full Paper

Synthesis, Anticonvulsant Activity, and SAR Study of Novel 4-Quinazolinone Derivatives

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Series of *N*-(4-substitutedphenyl)-4-(1-methyl (or 1,2-dimethyl)-4-oxo-1,2-dihydroquinazolin-3(4*H*)-yl)-alkanamides (**5a–j**) and 4-chloro-*N*′-((1-methyl (or 1,2-dimethyl)-4-oxo-1,2-dihydroquinazolin-3(4*H*)-yl)-alkaloyl)benzohydrazides (**6a–f**) were designed based on the previously reported essential structural features for anticonvulsant activity. Several amino acids were incorporated within the synthesized quinazolin-4(3*H*)-ones to improve their bioavailability and the anticonvulsant activity. Synthesis of the target compounds was accomplished in four steps starting from the reaction between *N*-methyl isatoic anhydride and the appropriate amino acid. Then, the carboxylic acid group was utilized to synthesize the required final structures. The new quinazolinone derivatives were evaluated for their anticonvulsant activity according to the Anticonvulsant Drug Development (ADD) Program protocol. All the 16 new quinazolinones exhibited good anticonvulsant activity; especially **5f**, **5b**, and **5c** showed superior anticonvulsant activities in comparison to the reference drug, with ED_{50} values of 28.90, 47.38, and 56.40 mg/kg, respectively.

Keywords: Amino acids / Anticonvulsant / Quinazolin-4(3*H*)-ones

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Introduction

Epilepsy is a state of chronic, unprovoked seizures, suggesting that the brain has become permanently altered to support abnormal neuronal firing [1].

Till the moment, although several antiepileptic drugs (AEDs) have been discovered, approximately one third of patients are still suffering from poor seizure control [1, 2]. The biggest challenge in epilepsy treatment is AEDs therapy resistance. In which, if developed, treatment may not be able to end seizures for a period of 12 months [3]. The major difficulty arises from the unknown mechanism of AEDs resistance [3, 4]. Moreover, the effectiveness of the available marketed drugs is largely compromised by notable adverse effects in patients [2]. Neurotoxicity, impaired memory function, symptoms of depression with life threatening hepatotoxicity, and megaloblastic anemia are examples of such adverse effects [5–7].

Thus, getting safer, more selective and more effective AEDs will remain the goal of the future research in medicinal chemistry [8, 9].

The diverse chemical structures of AEDs make it difficult to find a common pharmacophore for anticonvulsant activity. However, the conformational analysis of already biologically active AEDs as barbituric acids, hydantoin, succinamids can accelerate the common features for anticonvulsant activity. These features can be summarized in the presence of two aromatic rings with another region containing a number of hydrogen bonding groups, which seem to be of less significance than the correct conformational arrangement of the hydrophobic components [10].

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The quinazolin-4(3*H*)-one nucleus constitutes a hopeful chemical moiety affecting the central nervous system with its anticonvulsant effect [11]. 2-Methyl-3-*o*-tolyl-4(3*H*)-quinazolinone (methaqualone, **I**) (Fig. 1) represents a significant turning point in the field of synthetic anticonvulsant and prototype sedative-hypnotic containing quinazolinone ring system [12].

A literature survey concerning quinazolin-4(3*H*)-one nucleus-based anticonvulsants implied that alteration in its substituents has led to the generation of many CNS active agents [11–21]. Several natural and synthetic quinazolin-4(3*H*)-one compounds with a substituent at 1-position that is not likely present in the prototype methaqualone retain neuroprotective propriety and hence anticonvulsant activity (**II** and **III**) [13, 22]. In addition, it has been reported that if the 2-position is substituted with a substituent other than methyl group or even if not substituted, compounds will still have CNS depressant activity (**II–IV**) [11, 17, 22]. Compounds with hydrogen bonding region at 3-position are proven as a good lead for anticonvulsant activity (**IV**) [13, 17] (Fig. 1).

Herein, we designed a series of quinazolin-4-ones that keep the essential structural anticonvulsant features reported in various references [11, 13, 14, 17, 23], as hydrophobic binding unit, electron donor group and hydrogen bonding domain as shown in Fig. 2. At the same time, we attempted to understand the effect of substitution at 2-position as well as the effect of the length of the 3-position hydrogen bonding area on the anticonvulsant activity of quinazolin-4(3*H*)-one-derived compounds (Fig. 2).

We also incorporated different amino acids, which are D-alanine, β-alanine, and γ-aminobutyric acid (GABA) with quinazolin-4(3*H*)-one as a trial to improve its bioavailability and hence enhancing its anticonvulsant activity [24] and this enables us to separate the quinazolinone ring from the hydrogen bonding area by one, two, or three atoms distance, respectively, to identify the optimum distance for the anticonvulsant activity (Fig. 2).

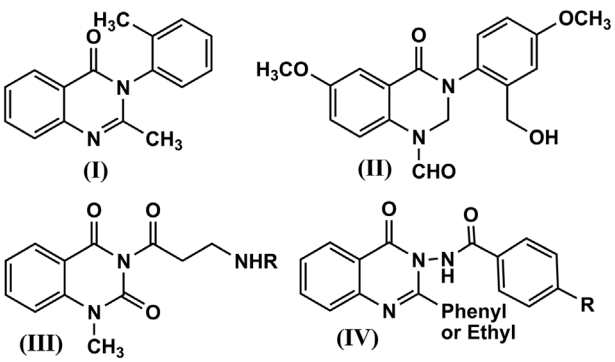


Figure 1. Methaqualone (**I**) and structures of some reported quinazolinone derivatives (**II–IV**) with anticonvulsant activity.

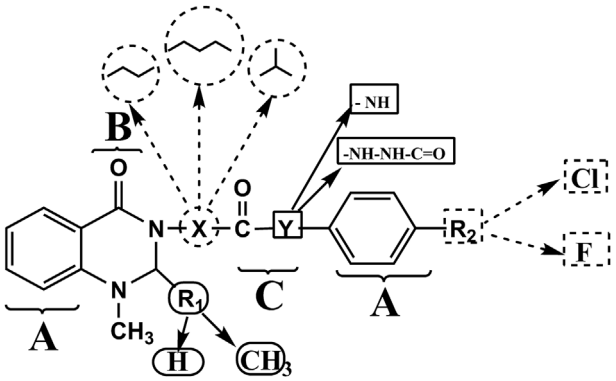


Figure 2. Structures and design strategy of target compounds based on the previously reported anticonvulsant structural features of quinazolinones. (A) Hydrophobic unit, (B) electron donor group, (C) hydrogen donor/acceptor unit.

Results and discussion

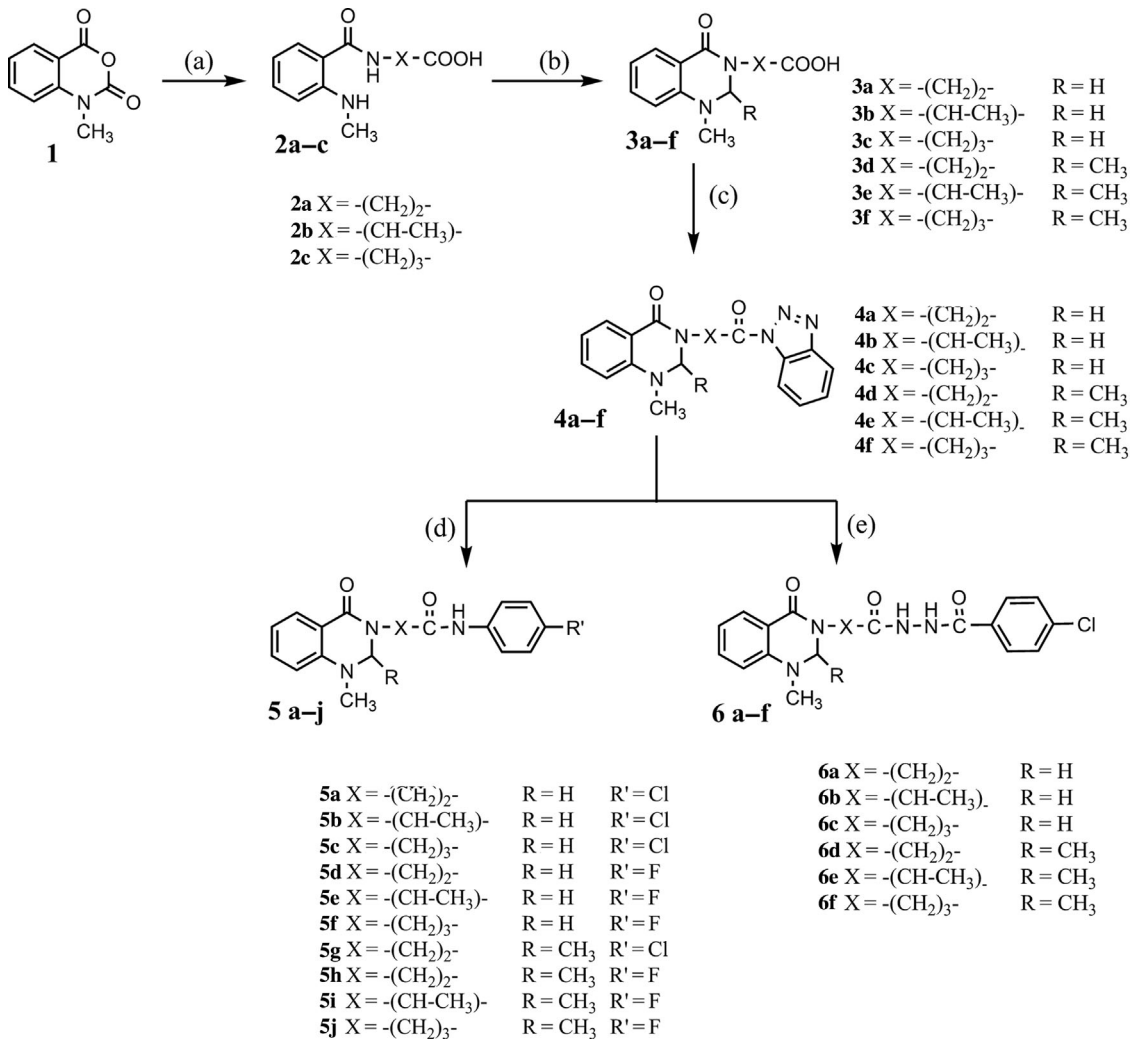
Chemistry

Compounds **5a–j** and **6a–f** were synthesized according to Scheme 1. Appropriate amino acid was allowed to react with *N*-methyl isatoic anhydride at 40–50°C in water containing triethylamine to yield the benzamidocarboxylic acids **2a–c**. Then cyclization of these intermediates (**2a–c**) with the appropriate aldehyde formed the (4-oxo-1,2-dihydroquinazolin-3(4*H*)-yl)carboxylic acids **3a–f**. These acids (**3a–f**) were then converted into the acyl benzotriazole analogs **4a–f** using 1*H*-benzotriazole and $SOCl_2$ at room temperature in dry DCM. The final compounds (**5a–j** and **6a–f**) were obtained by coupling the acyl benzotriazole derivatives (**5a–j** and **6a–f**) with either 4-substituted anilines or *p*-chlorobenzoic acid hydrazide using triethylamine in dry THF at room temperature for 4 h.

Pharmacology

Anticonvulsant screening

Based on the Anticonvulsant Drug Development (ADD) Program protocol [25], the final synthesized compounds (**5a–j** and **6a–f**) were subjected to anticonvulsant screening. This involves using the gold standard animal seizure models that could be used in early screening stages, the maximal electroshock seizure (MES) and the subcutaneous pentylenetetrazol seizure (scPTZ) animal models. The MES test pharmacological profile is proposed to be useful in indicating the drug's utility in generalized tonic–clonic seizures in humans. This test is thought to be sensitive to sodium channel inhibitors such as phenytoin. When tested compounds show activity in the MES test this suggests possessing voltage-gated ion channels inhibitory activity, while the scPTZ test pharmacological profile is thought to be effective in identifying drug's utility in generalized absence seizures in humans. Pentylenetetrazole is thought to inhibit GABA



Scheme 1. Synthetic route of the target compounds. Reagents and conditions: (a) Appropriate amino acid, NEt_3, H_2O, 40–50°C, 5 h, then acidified using 1 N HCl; (b) appropriate aldehyde, ethanol/water (2:3), reflux, 2 h; (c) 1*H*-benzotriazole, CH_2Cl_2, $SOCl_2$, rt, 4.5 h; (d) 4-substituted aniline, NEt_3, THF, rt, 24 h; (e) *p*-chlorobenzoic acid hydrazide, NEt_3, THF, rt, 24 h.

neurotransmission, thus producing seizures. When tested compounds show activity in this test this suggests possessing GABAerging activity enhancement activity [26–29].

The compounds **5a–j** and **6a–f** were administered intraperitoneally (i.p.) into the mice using doses of 30, 100, and 300 mg/kg and the observations were taken at two different time intervals (0.5 and 4 h). Neurotoxicity was measured by the rotarod test. The calculated Log *p*-values were calculated using the ACD lab version 8.0 software. The results are shown in Table 1.

The preliminary pharmacological screening indicated that all synthesized compounds **5a–j** and **6a–f** showed anticonvulsant activity in i.p. MES and/or scPTZ screenings. In the scPTZ test, compounds **5c** and **5f** were active at a dose of 30 mg/kg, whereas compounds **5a**, **5b**, **5d**, **6a**, and **6b** were active at a dose of 100 mg/kg and compounds **5h**, **5i**, **6c**, **6d**, and **6f** showed activity at 300 mg/kg dose level. Compounds **5h**, **6c**, **6d**, and **6f** became active after 0.5 h and did not show protection after 4 h, while compounds **5a–d**, **5f**, **5i**, **6a**, and **6b** were active at both time points. Moreover, in MES test compound **5b** showed protection at 30 mg/kg, compounds **5a**, **5e**, and **6d** protection was at 100 mg/kg, and compounds **5g**, **5i**, **5j**, **6a**, **6b**, **6e**, and **6f** needed 300 mg/kg dose level to protect against MES-induced seizures. Compounds **5b**, **5e**, **5i**, **6e**, and **6f** were active after 0.5 h while compounds **5a**, **5g**, **5j**, **6a**, **6b**, and **6d** were active at both time points. There is no obvious connection between the relative lipophilicity and the anticonvulsant activity of the target compounds, suggesting

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Table 1. **Preliminary screening results.**

Compound	Intraperitoneal injection in mice[a)]						Log *p*[e)]
	MES screening[b)]		scPTZ screening[c)]		NT screening[d)]		
	0.5 h	4 h	0.5 h	4 h	0.5 h	4 h	
5a	300	100	300	100	–	–	3.09
5b	30	–	100	300	300	–	3.29
5c	–	–	30	30	–	–	3.37
5d	–	–	100	100	–	–	2.69
5e	100	–	–	–	–	–	2.89
5f	–	–	30	100	300	–	2.97
5g	300	300	–	–	–	–	3.34
5h	–	–	300	–	–	–	2.94
5i	300	–	300	300	100	–	3.14
5j	300	300	–	–	–	–	3.22
6a	300	300	100	300	–	–	2.56
6b	300	300	100	300	100	–	2.76
6c	–	–	300	–	–	–	2.84
6d	100	100	300	–	–	–	2.8
6e	300	–	–	–	300	–	3
6f	300	–	300	–	–	–	3.08

[a)] Doses of 30, 100, and 300 mg/kg were administered. Each group consists of four animals. The animals were examined at 0.5 and 4.0 h after injection was made. The dash (–) indicates the absence of activity at maximum dose administered (300 mg/kg).
[b)] Maximal electroshock test.
[c)] Subcutaneous pentylenetetrazole test.
[d)] Neurotoxicity screening (rotarod test).
[e)] Log *p* was calculated using ACD lab version 8.0.

that other factors are involved. Results from neurotoxicity test revealed that compounds **5i** and **6b** caused neurotoxicity at 100 mg/kg and compounds **5b**, **5f**, and **6e** became neurotoxic at 300 mg/kg dose level. Other compounds did not show neurotoxicity at the maximum administered dose (300 mg/kg).

Standing on the primary pharmacological screening (Phase I) results, compounds **5a–f**, **6a**, and **6d** were subjected to quantitative studies (Phase II) to determine the pharmacological parameters, median effective dose (ED_{50}), median toxic dose (TD_{50}), and therapeutic index (PI). Time of peak effect (TPE) for each of these compounds was estimated and used for quantitative studies tests. Compounds **5f**, **5b**, and **5c** showed the lowest ED_{50} among other compounds with values of 28.90, 47.38, 56.40 mg/kg, respectively. All compounds tested in this phase showed high TD_{50} of more than 500 mg/kg. Compound **5f** showed therapeutic index of more than 17.30 that indicates highly safe anticonvulsant therapy. The results are shown in Table 2.

Structure–activity relationship (SAR)

All synthesized compounds (**5a–j** and **6a–f**) were designed to follow the aforementioned structural requirements.

The preliminary pharmacological screening inferred several SAR conclusions. It is obvious that **5a–j** series possesses higher activity than **6a–f** series. This may be due to longer hydrogen bonding linker in **6a–f** series comparing with that of **5a–j** series. Surprisingly, compounds with no substituent in 2-position, i.e. **5a–f** and **6a**, have higher activity compared to 2-methyl-substituted analogs, indicating the non-essential role of 2-position substituent in quinazolin-4(3*H*)-one derivatives to be active as anticonvulsant agents. Branching in the substituent at 3-position is undesired as compounds with D-alanine in their structure showed more neurotoxicity than these with β-alanine or γ-aminobutyric acid (GABA) in their structures. Within **5a–j** series, compounds with GABA linker showed better activity than those with other amino acid linker. This may be due to the increase in their lipophilicity. While, within **6a–f** series, compounds with β-alanine amino acid linker were more active, suggesting that the length of the hydrogen-bonding domain has an important impact on the activity. Compound **5f** with GABA linker at position 3 and with no substituent at position 2 showed the lowest ED_{50} of 28.90 mg/kg and the highest therapeutic index PI of more than 17.30.

Conclusion

In summary, a series of *N*-(4-substitutedphenyl)-4-(1-methyl (or 1,2-dimethyl)-4-oxo-1,2-dihydroquinazolin-3(4*H*)-yl)alkanamides (**5a–j**) and 4-chloro-*N*′-((1-methyl (or 1,2-dimethyl)-4-oxo-1,2-dihydroquinazolin-3(4*H*)yl)alkaloyl)benzohydrazides (**6a–f**) were designed, synthesized, and evaluated for their

Table 2. Quantitative study results.

Compound	TPE[a] (h)	ED_{50} MES[b] (mg/kg)	ED_{50} scPTZ[b] (mg/kg)	TD_{50} (mg/kg)	PI[c] (TD_{50}/ED_{50})
5a	1.0	ND[d]	123.6 (98.0–155.9)	>500	>4.05 (scPTZ)
5b	1.0	47.38 (25.67–87.45)	ND	>500	>10.55 (MES)
5c	1.0	ND	56.40 (28.45–111.80)	>500	>8.87 (scPTZ)
5d	1.0	ND	128.1 (81.29–201.8)	>500	>3.90 (scPTZ)
5e	0.5	128.5 (85.88–192.3)	ND	>500	>3.89 (MES)
5f	1.0	ND	28.90 (15.87–52.62)	>500	>17.30 (scPTZ)
6a	1.0	ND	135.2 (106.6–171.5)	>500	>3.70 (scPTZ)
6d	1.0	180.2 (105.0–307.6)	ND	>500	>2.77 (MES)
Phenytoin[e]	1.0	6.34 (3.55–11.34)	>500	44.42 (31.95–61.75)	5.56 (MES)
Ethosuximide[e]	0.25	>500	121.8 (69.54–213.4)	291.5 (242–350.5)	2.26 (scPTZ)

[a] Time of peak effect.
[b] Number of animals used: six; results are represented as mean ± SEM at 95% confidence limit (MES, maximum electroshock test; scPTZ, subcutaneous pentylenetetrazol test).
[c] Protective index (TD_{50}/ED_{50}).
[d] ND, not done.
[e] Reference AEDs tested in the same conditions.

anticonvulsant activity using both MES and scPTZ screens. In addition, they were evaluated for their neurotoxicity using rotarod test. All compounds showed good anticonvulsant activity with minimum levels of neurotoxicity. In this study, we prove the non-essentiality of 2-position substituent in quinazolin-4(3*H*)-one derivatives to be active as anticonvulsant agents. Hydrogen bonding region length plays an important role in determination of quinazolin-4(3*H*)-one derivatives anticonvulsant activity. The most active compounds are **5b**, **5c**, and **5f** with ED_{50} 47.38, 56.40, and 28.90 mg/kg, respectively. Compound **5f** has therapeutic index >17.30 that indicates high safety margin.

Experimental

Chemistry

General

Melting points (°C) were measured on a Gallenkamp melting point apparatus (London, UK), and are uncorrected. NMR spectra were performed in the Microanalytical Center, Faculty of Pharmacy, Cairo University, Egypt or Microanalytical Center, Faculty of Science, Zagazig University, Egypt. Elemental analyses were performed in the Microanalytical Center, Faculty of Science, Cairo University, Egypt, or in the Regional Center for Mycology and Biotechnology, Al-Azhar University, Egypt. Mass spectra were performed in the the Microanalytical Center, Faculty of Science, Cairo University, Egypt. NMR spectra were recorded on a Bruker high performance Digital FT-NMR spectrometer Avance III 400 MHz using dimethyl sulfoxide (DMSO)-d_6 and chloroform ($CDCl_3$)-*d* as solvent and tetramethylsilane (TMS) as an internal standard (chemical shift in δ, ppm). Mass spectra were determined using a GC/MS Shimadzu Qp-2010 plus (Shimadzu Corporation, Tokyo, Japan). Elemental analyses were determined using the Vario EL-III (Elementar) CHNS analyzer (Hanau, Germany). All reactions were monitored by thin layer chromatography (TLC) using silica gel 60 GF245 (E-Merck, Germany) and were visualized by UV-lamp at wavelength (λ) 254 nm.

^{1}H and ^{13}C NMR spectra as well as the InChI codes of the investigated compounds together with some biological activity data are provided as Supporting Information.

*Synthesis of compounds **2a–c***

Compounds **2a–c** (2-(methylamino)benzamido)carboxylic acids) were synthesized according to previously reported procedures [30].

*General method for the synthesis of (1-methyl (or 1,2-dimethyl)-4-oxo-1,2-dihydroquinazolin-3(4H)-yl)-carboxylic acids (**3a–f**)*

A mixture of benzamidocarboxylic acid (**2a–c**, 0.018 mol) and appropriate aldehyde (0.18 mol) in ethanol/water (2:3) was heated under reflux for 2 h, then ethanol was evaporated and the reaction mixture was allowed to cool. The product crystals that formed were collected under vacuum and washed with water and petroleum ether to provide the (4-oxo-1,2-dihydroquinazolin-3(4*H*)-yl)carboxylic acid (**3a–f**) in 59.7–91.89% yield and sufficient purity for the next step.

*3-(1-Methyl-4-oxo-1,2-dihydroquinazolin-3(4H)-yl)-propanoic acid (**3a**)*

(63.29% yield). M.p.: 144–147°C. ^{1}H NMR (DMSO-d_6) δ 2.55 (2H, t, *J* 7.2, CH_2CO), 2.82 (3H, s, NCH_3), 3.62 (2H, t, *J* 7.2, $N\underline{CH_2}CH_2CO$), 4.49 (2H, s, NCH_2N), 6.77–6.85 (2H, m, H-6, H-8), 7.39 (1H, t, *J* 8, H-7), 7.72 (1H, dd, *J* 8, H-5), 12.29 (1H, s, COOH exch.).

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*2-(1-Methyl-4-oxo-1,2-dihydroquinazolin-3(4H)-yl)-propanoic acid (**3b**)*
(63.29% yield). M.p.: 191–193°C. ^{1}H NMR (DMSO-d_6) δ 1.43 (3H, d, *J* 7.2, COCH$\underline{CH_3}$), 2.86 (3H, s, NCH_3), 4.47–4.52 (2H, m, NCH_2N), 4.91–4.96 (1H, m, CO$\underline{CH}CH_3$), 6.81–6.86 (2H, m, H-6, H-8), 7.41 (1H, t, *J* 7.2, H-7), 7.73 (1H, d, *J* 6.4, H-5), 12.83 (1H, s, COOH exch.).

*4-(1-Methyl-4-oxo-1,2-dihydroquinazolin-3(4H)-yl)-butanoic acid (**3c**)*
(67.62% yield). M.p.: 128–131°C. ^{1}H NMR (DMSO-d_6) δ 1.76–1.81 (2H, m, $COCH_2\underline{CH_2}CH_2$), 2.24 (2H, t, *J* 7.2, $\underline{COCH_2}CH_2CH_2$), 2.83 (3H, s, NCH_3), 3.44 (2H, t, *J* 6.8, $COCH_2CH_2\underline{CH_2}$), 4.45 (2H, s, NCH_2N), 6.78–6.85 (2H, m, H-6, H-8), 7.39 (1H, t, *J* 7.2, H-7), 7.72 (1H, d, *J* 7.2, H-5), 12.08 (1H, s, COOH).

*3-(1,2-Dimethyl-4-oxo-1,2-dihydroquinazolin-3(4H)-yl)-propanoic acid (**3d**)*
(59.7% yield). M.p.: 156–159°C. ^{1}H NMR (DMSO-d_6) δ 1.13 (3H, d, *J* 6, NCH$\underline{CH_3}$), 2.50–2.57 (1H, m, CH_2CO), 2.60–2.67 (1H, m, CH_2CO), 2.82 (3H, s, NCH_3), 3.16–3.23 (1H, m, $\underline{NCH_2}CH_2CO$), 3.88–3.95 (1H, m, $\underline{NCH_2}CH_2CO$), 4.88–4.93 (1H, m, N$\underline{CH}CH_3$), 6.69 (1H, d, *J* 8, H-8), 6.77 (1H, t, *J* 7.6, H-6), 7.37 (1H, t, *J* 8, H-7), 7.68 (1H, dd, *J* 7.6, H-5), 12.32 (1H, s, COOH exch.).

*2-(1,2-Dimethyl-4-oxo-1,2-dihydroquinazolin-3(4H)-yl)-propanoic acid (**3e**)*
(59.7% yield). M.p.: 172–174°C. ^{1}H NMR ($CDCl_3$) δ 1.31 (3H, d, *J* 6, NCH$\underline{CH_3}$), 1.63 (3H, d, *J* 7.2, COCH$\underline{CH_3}$), 2.96 (3H, s, NCH_3), 4.82–4.91 (1H, m, N$\underline{CH}CH_3$+ CO$\underline{CH}CH_3$), 6.70 (1H, d, *J* 8.2, H-8), 6.91 (1H, t, *J* 7.4, H-6), 7.46 (1H, t, *J* 8.6, H-7), 7.96 (1H, dd, *J* 7.6, H-5).

*4-(1,2-Dimethyl-4-oxo-1,2-dihydroquinazolin-3(4H)-yl)-butanoic acid (**3f**)*
(91.89% yield). M.p.: 124–126°C. ^{1}H NMR ($CDCl_3$) δ 1.27 (3H, d, *J* 6, NCH$\underline{CH_3}$), 1.98–2.06 (2H, m, $COCH_2\underline{CH_2}CH_2$), 2.44–2.49 (2H, m, $\underline{COCH_2}CH_2CH_2$), 2.92 (3H, s, NCH_3), 3.01–3.08 (1H, m, $COCH_2CH_2\underline{CH_2}$), 4.05–4.12 (1H, m, $COCH_2CH_2\underline{CH_2}$), 4.63–4.67 (1H, m, $\underline{CH}CH_3$), 6.66 (1H, d, *J* 8, H-8), 6.88 (1H, t, *J* 7.2, H-6), 7.41 (1H, t, *J* 8.4, H-7), 7.94 (1H, dd, *J* 7.6, H-5).

*General method for the synthesis of 3-(1H-benzo[d][1,2,3]-triazol-1-yl)-3-oxoalkyl)-1-methyl (or 1,2-dimethyl)-2,3-dihydroquinazolin-4(1H)-one (**4a–f**)*
To a solution of 1*H*-benzotriazole (3.57 g, 0.03 mol) in anhydrous dichloromethane, thionylchloride (1.43 g, 0.012 mol) was added and the reaction mixture was stirred at room temperature for 30 min, then the (4-oxo-1,2-dihydroquinazolin-3(4*H*)-yl)carboxylic acids (**3a–f**, 0.01 mol) were added and the reaction mixture was stirred at room temperature for a further 4 h. The precipitate formed was filtered off and the organic layer was extracted twice with 5% Na_2CO_3 solution, washed with water, and dried over anhydrous sodium sulfate, then the solvent was removed *in vacuo* to obtain the desired *N*-acylbenzotriazole (**4a–f**) in 35.40–79.96% yield and sufficient purity for use in the next step.

*3-(3-(1H-Benzo[d][1,2,3]triazol-1-yl)-3-oxopropyl)-1-methyl-2,3-dihydroquinazolin-4(1H)-one (**4a**)*
(70.18% yield). M.p.: 139–141°C. ^{1}H NMR ($CDCl_3$) δ 2.93 (3H, s, $NC\underline{H_3}$), 3.90 (2H, t, *J* 8, $C\underline{H_2}CO$), 4.09 (2H, t, *J* 8, $N\underline{CH_2}CH_2CO$), 4.67 (2H, s, $N\underline{CH_2}N$), 6.75 (1H, d, *J* 8.2, H-8), 6.92 (1H, t, *J* 7.6, H-6), 7.40 (1H, t, *J* 8.6, ArH), 7.53 (1H, t, *J* 8, ArH), 7.68 (1H, t, *J* 8, H-7), 7.96 (1H, dd, *J* 7.6, H-5), 8.15 (1H, d, *J* 8.4, ArH), 8.31 (1H, d, *J* 8, ArH).

*3-(1-(1H-Benzo[d][1,2,3]triazol-1-yl)-1-oxopropan-2-yl)-1-methyl-2,3-dihydroquinazolin-4(1H)-one (**4b**)*
(35.09% yield). M.p.: 133–136°C. ^{1}H NMR ($CDCl_3$) δ 1.88 (3H, d, *J* 7.2, COCH$\underline{CH_3}$), 2.95 (1H, bs, CO$\underline{CH}CH_3$), 3.03 (3H, s, NCH_3), 4.76 (1H, d, *J* 9.2, NCH_2N), 4.91 (1H, d, *J* 9.2, NCH_2N), 6.80 (1H, d, *J* 8, H-8), 6.91 (1H, t, *J* 7.6, H-6), 7.44 (1H, t, *J* 8.5, ArH), 7.54 (1H, t, *J* 8, ArH), 7.68 (1H, t, *J* 7.6, H-7), 7.91 (1H, dd, *J* 8, H-5), 8.13 (1H, d, *J* 8.4, ArH), 8.27 (1H, d, *J* 8.4, ArH).

*3-(4-(1H-Benzo[d][1,2,3]triazol-1-yl)-4-oxobutyl)-1-methyl-2,3-dihydroquinazolin-4(1H)-one (**4c**)*
(83.93% yield). M.p.: 115–117°C. ^{1}H NMR ($CDCl_3$) δ 2.22–2.29 (2H, m, $COCH_2\underline{CH_2}CH_2$), 2.84 (3H, s, NCH_3), 3.15 (2H, t, *J* 6.8, $\underline{COCH_2}CH_2CH_2$), 3.71 (2H, t, *J* 6.8, $COCH_2CH_2\underline{CH_2}$), 4.45 (2H, s, NCH_2N), 6.62 (1H, d, *J* 8.4, H-8), 6.84 (1H, t, *J* 7.2, H-6), 7.33 (1H, t, *J* 7.6, ArH), 7.47 (1H, t, *J* 7.6, ArH), 7.61 (1H, t, *J* 7.7, H-7), 7.90 (1H, d, *J* 7.6, H-5), 8.08 (1H, d, *J* 8.4, ArH), 8.23 (1H, d, *J* 8.4, ArH).

*3-(3-(1H-Benzo[d][1,2,3]triazol-1-yl)-3-oxopropyl)-1,2-dimethyl-2,3-dihydroquinazolin-4(1H)-one (**4d**)*
(80.36% yield). Semisolid product. ^{1}H NMR ($CDCl_3$) δ 1.36 (3H, d, *J* 6, NCH$\underline{CH_3}$), 2.93 (3H, s, NCH_3), 3.53–3.60 (1H, m, CH_2CO), 3.77–3.84 (1H, m, CH_2CO), 4.03–4.11 (1H, m, $N\underline{CH_2}CH_2CO$), 4.44–4.49 (1H, m, $N\underline{CH_2}CH_2CO$), 4.96–5.01 (1H, m, N$\underline{CH}CH_3$), 6.69 (1H, d, *J* 8.4, H-8), 6.89 (1H, t, *J* 7.6, H-6), 7.40 (1H, t, *J* 8.4, ArH), 7.53 (1H, t, *J* 7.6, ArH), 7.68 (1H, t, *J* 8, H-7), 7.95 (1H, dd, *J* 7.6, H-5), 8.14 (1H, d, *J* 8.4, ArH), 8.31 (1H, d, *J* 8.4, ArH).

*3-(4-(1H-Benzo[d][1,2,3]triazol-1-yl)-4-oxobutyl)-1,2-dimethyl-2,3-dihydroquinazolin-4(1H)-one (**4f**)*
(96.36% yield). M.p.: 110–111°C. ^{1}H NMR ($CDCl_3$) δ 1.31 (3H, d, *J* 6, NCH$\underline{CH_3}$), 2.27–2.41 (2H, m, $COCH_2\underline{CH_2}CH_2$), 2.89 (3H, s, NCH_3), 3.07–3.14 (1H, m, $COCH_2CH_2\underline{CH_2}$), 3.55 (2H, t, *J* 7.2, $\underline{COCH_2}CH_2CH_2$), 4.26–4.33 (1H, m, $COCH_2CH_2\underline{CH_2}$), 4.68–4.72 (1H, m, N$\underline{CH}CH_3$), 6.61 (1H, d, *J* 8.4, H-8), 6.87 (1H, t, *J* 7.2, H-6), 7.37 (1H, t, *J* 8.4, ArH), 7.51 (1H, t, *J* 7.6, ArH), 7.65 (1H, t, *J* 7.2, H-7), 7.94 (1H, dd, *J* 7.6, H-5), 8.13 (1H, d, *J* 8.4, ArH), 8.28 (1H, d, *J* 8, ArH).

*General method for the synthesis of N-(4-substitutedphenyl)-4-(1-methyl (or 1,2-dimethyl)-4-oxo-1,2-dihydroquinazolin-3(4H)-yl)alkanamides (**5a–j**)*
A solution of *N*-acylbenzotriazole derivative (**4a–f**, 0.005 mol) and the 4-substituted aniline (0.005 mol) in anhydrous THF

containing triethyl amine (0.76 g, 0.0075 mol) was stirred at room temperature for 24 h, then THF was evaporated under reduced pressure and the residue was then treated with appropriate method suitable for each.

The residue was washed with diethyl ether and the produced solid is filtered off and washed with ether twice as in **5a**, **5d**, and **5h**.

Or the residue was then dissolved in dichloromethane and extracted twice with 5% Na_2CO_3 solution then 1 N HCl solution, then the organic layer was washed with water and dried with anhydrous sodium sulfate and the solvent was evaporated under reduced pressure as in **5b**, **5e**, **5g**, and **5i**.

Or the residue was then dissolved in methanol and boiled for 5 min, the methanol was evaporated and then the residue was dissolved in dichloromethane and extracted twice with 5% Na_2CO_3 solution then 1 N HCl solution, then the organic layer was washed with water and dried with anhydrous sodium sulfate and the solvent was evaporated under reduced pressure as in **5c**, **5f**, and **5j**. This step afforded the desired products in a 35–53% yield.

*N-(4-Chlorophenyl)-3-(1-methyl-4-oxo-1,2-dihydroquinazolin-3(4H)-yl)propanamide (**5a**)*
(46.75% yield). M.p.: 220–223°C. ^{1}H NMR (DMSO-d_6) δ 2.67 (2H, t, *J* 6.8, CH_2CO), 2.79 (3H, s, NCH_3), 3.70 (2H, t, *J* 6.8, NCH_2CH_2CO), 4.49 (2H, s, NCH_2N), 6.77–6.85 (2H, m, H-6, H-8), 7.33–7.41 (3H, m, H-3′, H-5′, H-7), 7.60 (2H, d, *J* 8.8, H-2′, H-6′), 7.71 (1H, d, *J* 7.6, H-5), 10.15 (1H, s, CONH exch.). ^{13}C NMR ($CDCl_3$) δ 36.03 (CH_2CO), 36.59 (NCH_3), 42.67 (NCH_2), 67.62 (NCH_2N), 112.50 (ArCH), 117.34 (ArCH), 119.42 (ArCH), 121.16 (ArCH), 128.71 (ArCH), 128.86 (ArCH), 129.04 (ArC), 134.00 (ArC), 136.91 (ArC), 149.19 (ArC), 164.46 (ArC), 169.37 (ArC). MS, *m/z*: 343 (M^+), 345 (M^++2). Anal. calcd. for $C_{18}H_{18}ClN_3O_2$: C, 62.88; H, 5.28; N, 12.22. Found: C, 62.61; H, 5.00; N, 12.13.

*N-(4-Chlorophenyl)-2-(1-methyl-4-oxo-1,2-dihydroquinazolin-3(4H)-yl)propanamide (**5b**)*
(36% yield). M.p.: 161–163°C. ^{1}H NMR (DMSO-d_6) δ 1.47 (3H, d, *J* 7.2, $COCHCH_3$), 2.88 (3H, s, NCH_3), 4.58 (1H, d, *J* 9.6, NCH_2N), 4.64 (1H, d, *J* 9.6, NCH_2N), 5.19–5.24 (1H, m, $COCHCH_3$), 6.82–6.87 (2H, m, H-6, H-8), 7.35–7.44 (3H, m, H-3′, H-5′, H-7), 7.63 (2H, d, *J* 8.8, H-2′, H-6′), 7.74 (1H, d, *J* 7.7, H-5), 10.27 (1H, s, CONH, exch.). ^{13}C NMR ($CDCl_3$) δ 13.69 ($COCHCH_3$), 36.33 (NCH_3), 51.66 ($COCHCH_3$), 62.64 (NCH_2N), 112.65 (ArCH), 117.31 (ArCH), 119.47 (ArCH), 121.12 (ArCH), 128.91 (ArCH), 129.21 (ArCH), 129.25 (ArC), 134.21 (ArC), 136.50 (ArC), 149.47 (ArC), 164.64 (ArC), 169.22 (ArC). MS, *m/z*: 343 (M^+), 345 (M^++2). Anal. calcd. for $C_{18}H_{18}ClN_3O_2$: C, 62.88; H, 5.28; N, 12.22. Found: C, 62.91; H, 5.52; N, 12.47.

*N-(4-Chlorophenyl)-4-(1-methyl-4-oxo-1,2-dihydroquinazolin-3(4H)-yl)butanamide (**5c**)*
(26.46% yield). M.p.: 88–91°C. ^{1}H NMR ($CDCl_3$) δ 2.02–2.07 (2H, m, $COCH_2CH_2CH_2$), 2.41 (2H, t, *J* 6, $COCH_2CH_2CH_2$), 2.91 (3H, s, NCH_3), 3.68 (2H, t, *J* 6, $COCH_2CH_2CH_2$), 4.46 (2H, s, NCH_2N), 6.70 (1H, d, *J* 8.4, H-8), 6.94 (1H, t, *J* 7.6, H-6), 7.28 (2H, d, *J* 8.8, H-3′, H-5′), 7.44 (1H, t, *J* 7.8, H-7), 7.66 (2H, d, *J* 8.8, H-2′, H-6′), 7.99–8.01 (1H, d, *J* 7.7, H-5), 9.59 (1H, s, CONH, exch.). ^{13}C NMR ($CDCl_3$) δ 24.41 ($COCH_2CH_2CH_2$), 34.57 ($COCH_2CH_2CH_2$), 35.93 (NCH_3), 44.39 ($COCH_2CH_2CH_2$), 66.44 (NCH_2N), 112.21 (ArCH), 117.22 (ArCH), 119.22 (ArCH), 120.98 (ArCH), 128.51 (ArCH), 128.73 (ArCH), 128.98 (ArC), 133.94 (ArC), 137.33 (ArC), 149.22 (ArC), 164.84 (ArC), 171.26 (ArC). MS, *m/z*: 357 (M^+), 359 (M^++2). Anal. calcd. for $C_{19}H_{20}ClN_3O_2$: C, 63.77; H, 5.63; N, 11.74. Found: C, 63.48; H, 5.50; N, 11.71.

*N-(4-Fluorophenyl)-3-(1-methyl-4-oxo-1,2-dihydroquinazolin-3(4H)-yl)propanamide (**5d**)*
(35.62% yield). M.p.: 189–191°C. ^{1}H NMR ($CDCl_3$) δ 2.77 (2H, t, *J* 5.6, CH_2CO), 2.83 (3H, s, NCH_3), 3.86 (2H, t, *J* 5.6, NCH_2CH_2CO), 4.54 (2H, s, NCH_2N), 6.65 (1H, d, *J* 8.4, H-8), 6.82 (1H, t, *J* 7.6, H-6), 6.96 (2H, t, *J* 8.4, H-3′, H-5′), 7.37 (1H, t, *J* 7.6, H-7′), 7.57 (dd, *J* = 7.9, 5.2 H-2′, H-6′), 7.84 (1H, d, *J* 7.6, H-5), 9.25 (1H, s, CONH, exch.). ^{13}C NMR ($CDCl_3$) δ 35.96 (CH_2CO), 36.54 (NCH_3), 42.86 (NCH_2CH_2CO), 67.85 (NCH_2N), 112.38 (ArCH), 115.67 (ArCH), 117.47 (ArCH), 119.16 (ArCH), 121.82 (ArCH), 128.72 (ArCH), 133.98 (ArC), 134.63 (ArC), 149.63 (ArC), 160.54 (ArC), 164.53 (ArC), 169.55 (ArC). MS, *m/z*: 327 (M^+). Anal. calcd. for $C_{18}H_{18}FN_3O_2$: C, 66.04; H, 5.54; N, 12.84. Found: C, 65.79; H, 5.26; N, 13.01.

*N-(4-Fluorophenyl)-2-(1-methyl-4-oxo-1,2-dihydroquinazolin-3(4H)-yl)propanamide (**5e**)*
(35.41% yield). M.p.: 151–152°C. ^{1}H NMR ($CDCl_3$) δ 1.52 (3H, d, *J* 7.2, $COCHCH_3$), 2.91 (3H, s, NCH_3), 4.39–4.51 (2H, m, NCH_2N), 5.42–5.47 (1H, m, $COCHCH_3$), 6.73 (1H, d, *J* 8, H-8), 6.90–6.99 (3H, m, H-3′, H-5′, H-6), 7.40–7.49 (3H, m, H-2′, H-6′, H-7), 7.97 (1H, d, *J* 8, H-5), 8.73 (1H, s, CONH). ^{13}C NMR ($CDCl_3$) δ 13.60 ($COCHCH_3$), 36.40 (NCH_3), 51.67 ($COCHCH_3$), 62.76 (NCH_2N), 112.69 (ArCH), 115.59 (ArCH), 117.45 (ArCH), 119.54 (ArCH), 121.71 (ArCH), 129.42 (ArCH), 133.96 (ArC), 134.31 (ArC), 149.69 (ArC), 160.69 (ArC), 164.80 (ArC), 169.11 (ArC). MS, *m/z*: 327 (M^+). Anal. calcd. for $C_{18}H_{18}FN_3O_2$: C, 66.04; H, 5.54; N, 12.84. Found: C, 65.80; H, 5.85; N, 13.00.

*N-(4-Fluorophenyl)-4-(1-methyl-4-oxo-1,2-dihydroquinazolin-3(4H)-yl)butanamide (**5f**)*
(25.5% yield). M.p.: 104–107°C. ^{1}H NMR (DMSO-d_6) δ 1.85–1.88 (2H, m, $COCH_2CH_2CH_2$), 2.33 (2H, t, *J* 7.2, $COCH_2CH_2CH_2$), 2.83 (3H, s, NCH_3), 3.49 (2H, t, *J* 6.8, $COCH_2CH_2CH_2$), 4.47 (2H, s, NCH_2N), 6.78–6.85 (2H, m, H-6, H-8), 7.11 (2H, t, *J* 8.4, H-3′, H-5′), 7.39 (1H, t, *J* 8, H-7), 7.59 (2H, dd, *J* 8.0, 5.3, H-2′, H-6′), 7.72 (1H, d, *J* 7.6, H-5), 9.96 (1H, s, CONH, exch.). ^{13}C NMR (DMSO-d_6) δ 23.15 ($COCH_2CH_2CH_2$), 33.59 ($COCH_2CH_2CH_2$), 35.24 (NCH_3), 43.90 ($COCH_2CH_2CH_2$), 65.46 (NCH_2N), 112.30 (ArCH), 115.24 (ArCH), 117.28 (ArCH), 118.11 (ArCH), 120.77 (ArCH), 128.01 (ArCH), 133.21 (ArC), 135.68 (ArC), 149.62 (ArC), 158.97 (ArC), 162.42 (ArC), 170.49 (ArC). MS, *m/z*: 341 (M^+). Anal. calcd. for $C_{19}H_{20}FN_3O_2$: C, 66.85; H, 5.91; N, 12.31. Found: C, 67.08; H, 5.95; N, 12.49.

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*N-(4-Chlorophenyl)-3-(1,2-dimethyl-4-oxo-1,2-dihydroquinazolin-3(4H)-yl)-propanamide (**5g**)*
(44.16% yield). M.p.: 155–157°C. ^{1}H NMR (DMSO-d_6) δ 1.14 (3H, d, *J* 6, NCHC<u>H</u>$_3$), 2.60–2.66 (1H, m, CH_2CO), 2.70–2.76 (1H, m, CH_2CO), 2.78 (3H, s, NCH_3), 3.28–3.32 (1H, m, NC<u>H</u>$_2$CH$_2$CO), 3.94–4.01 (1H, m, NC<u>H</u>$_2$CH$_2$CO), 4.86–4.91 (1H, m, NC<u>H</u>CH$_3$), 6.67 (1H, d, *J* 8, H-8), 6.77 (1H, t, *J* 7.6, H-6), 7.33–7.39 (3H, m, H-3′, H-5′, H7), 7.60 (2H, d, *J* 8.8, H-2′, H-6′), 7.69 (1H, d, *J* 7.6, H-5), 10.14 (1H, s, CONH exch.). ^{13}C NMR ($CDCl_3$) δ 14.61 (NCH<u>C</u>H$_3$), 35.49 (<u>C</u>H$_2$CO), 36.83 (N<u>C</u>H$_3$), 41.82 (N<u>C</u>H$_2$CH$_2$CO), 73.63 (N<u>C</u>HCH$_3$), 112.75 (ArCH), 116.43 (ArCH), 118.33 (ArCH), 121.17 (ArCH), 128.15 (ArCH), 128.81 (ArCH), 134.06 (ArC), 137.23 (ArC), 146.55 (ArC), 163.25 (ArC), 169.72 (ArC). MS, *m/z*: 357 (M^+), 359 (M^++2). Anal. calcd. for $C_{19}H_{20}ClN_3O_2$: C, 63.77; H, 5.63; N, 11.74. Found: C, 63.90; H, 5.91; N, 11.88.

*3-(1,2-Dimethyl-4-oxo-1,2-dihydroquinazolin-3(4H)-yl)-N-(4-fluorophenyl)propanamide (**5h**)*
(53.42% yield). M.p.: 138–140°C. ^{1}H NMR ($CDCl_3$) δ 1.25 (3H, d, *J* 6, NCHC<u>H</u>$_3$), 2.69–2.74 (1H, m, CH_2CO), 2.81 (3H, s, NCH_3), 2.83–2.87 (1H, m, CH_2CO), 3.41–3.48 (1H, m, NC<u>H</u>$_2$CH$_2$CO), 4.13–4.19 (1H, m, NC<u>H</u>$_2$CH$_2$CO), 4.77–4.82 (1H, m, NC<u>H</u>CH$_3$), 6.59 (1H, d, *J* 8, H-8), 6.82 (1H, t, *J* 7.6, H-6), 6.98 (2H, t, *J* = 12.0, 5.4 H-3′, H-5′), 7.38 (1H, t, *J* = 7.8, H-7), 7.54 (2H, dd, *J* = 9.0, 4.9 H-2′, H-6′), 7.87 (1H, d, *J* = 7.7, H-5), 8.92 (1H, s, CONH exch.). ^{13}C NMR ($CDCl_3$) δ 14.58 (NCH<u>C</u>H$_3$), 35.40 (<u>C</u>H$_2$CO), 36.74 (N<u>C</u>H$_3$), 41.90 (N<u>C</u>H$_2$CH$_2$CO), 73.60 (N<u>C</u>HCH$_3$), 112.65 (ArCH), 115.85 (ArCH), 116.47 (ArCH), 118.22 (ArCH), 121.73 (ArCH), 128.17 (ArCH), 133.99 (ArC), 134.62 (ArC), 146.62 (ArC), 160.39 (ArC), 163.23 (ArC), 169.60 (ArC). MS, *m/z*: 341 (M^+). Anal. calcd. for $C_{19}H_{20}FN_3O_2$: C, 66.85; H, 5.91; N, 12.31. Found: C, 66.95; H, 6.05; N, 12.46.

*2-(1,2-Dimethyl-4-oxo-1,2-dihydroquinazolin-3(4H)-yl)-N-(4-fluorophenyl)propanamide (**5i**)*
(35.89% yield). M.p.: 150–153°C. ^{1}H NMR ($CDCl_3$) δ 1.17 (3H, d, *J* 6, NCHC<u>H</u>$_3$), 1.55 (3H, d, *J* 6.8, COCHC<u>H</u>$_3$), 2.92 (3H, s, NCH_3), 4.83–4.87 (1H, m, NC<u>H</u>CH$_3$), 5.27–5.33 (1H, m, COC<u>H</u>CH$_3$), 6.63 (1H, d, *J* 8.4, H-8), 6.87 (1H, t, *J* 7.6, H-6), 6.96–7.00 (2H, t, *J* 8.4, H-3′, H-5′), 7.42 (1H, t, *J* 7.6, H-7), 7.50 (2H, dd, *J* 8.1, 5.3, H-2′, H-6′), 7.97 (1H, d, *J* 8, H-5), 9.31 (1H, s, CONH). ^{13}C NMR ($CDCl_3$) δ 13.41 (COCH<u>C</u>H$_3$), 15.19 (NCH<u>C</u>H$_3$), 35.83 (N<u>C</u>H$_3$), 51.56 (CO<u>C</u>HCH$_3$), 68.69 (N<u>C</u>HCH$_3$), 112.81 (ArCH), 115.58 (ArCH), 115.87 (ArCH), 118.48 (ArCH), 121.71 (ArCH), 129.13 (ArCH), 134.19 (ArC), 134.72 (ArC), 146.41 (ArC), 160.59 (ArC), 164.45 (ArC), 169.72 (ArC). MS, *m/z*: 341 (M^+). Anal. calcd. for $C_{19}H_{20}FN_3O_2$: C, 66.85; H, 5.91; N, 12.31. Found: C, 67.02; H, 5.97; N, 12.47.

*4-(1,2-Dimethyl-4-oxo-1,2-dihydroquinazolin-3(4H)-yl)-N-(4-fluorophenyl)butanamide (**5j**)*
(28.57% yield). ^{1}H NMR ($CDCl_3$) δ 1.26 (3H, d, *J* 8, NCHC<u>H</u>$_3$), 2.02–2.05 (2H, m, COCH$_2$<u>C</u>H$_2$CH$_2$), 2.38 (2H, t, *J* 5.6, <u>C</u>OCH$_2$CH$_2$CH$_2$), 2.86 (3H, s, NCH_3), 3.04–3.10 (1H, m, COCH$_2$CH$_2$<u>C</u>H$_2$), 4.08–4.15 (1H, m, COCH$_2$CH$_2$<u>C</u>H$_2$), 4.58–4.63 (1H, m, NC<u>H</u>CH$_3$), 6.56 (1H, d, *J* 8.4, H-8), 6.85 (1H, t, *J* 7.6, H-6), 6.96 (2H, t, *J* 8.4, H-3′, H-5′), 7.37 (1H, t, *J* 7.6, H-7), 7.61 (2H, dd, *J* 7.7, 5.2, H-2′, H-6′), 7.93 (1H, d, *J* 7.6, H-5), 9.48 (1H, s, CONH). ^{13}C NMR ($CDCl_3$) δ 14.32 (NCH<u>C</u>H$_3$), 25.07 (COCH$_2$<u>C</u>H$_2$CH$_2$), 34.61 (CO<u>C</u>H$_2$CH$_2$CH$_2$), 35.56 (N<u>C</u>H$_3$), 43.46 (COCH$_2$CH$_2$<u>C</u>H$_2$), 72.40 (N<u>C</u>HCH$_3$), 112.61 (ArCH), 115.50 (ArCH), 116.61 (ArCH), 118.46 (ArCH), 121.49 (ArCH), 128.72 (ArCH), 134.14 (ArC), 134.95 (ArC), 146.61 (ArC), 160.31 (ArC), 163.82 (ArC), 171.26 (ArC). MS, *m/z*: 355 (M^+). Anal. calcd. for $C_{20}H_{22}FN_3O_2$: C, 67.59; H, 6.24; N, 11.82. Found: C, 67.56; H, 6.55; N, 11.51.

*General method for the synthesis of 4-chloro-N′-((1-methyl (or 1,2-dimethyl)-4-oxo-1,2-dihydroquinazolin-3(4H)-yl)-alkaloyl)benzohydrazides (**6a–f**)*
A solution of *N*-acylbenzotriazole derivative (**4a–f**, 0.005 mol) and *p*-chlorobenzoic acid hydrazide (0.85 g, 0.005 mol) in anhydrous THF containing triethyl amine (0.76 g, 0.0075 mol) was stirred at room temperature for 24 h, then THF was evaporated under reduced pressure. The residue was washed with diethyl ether, the formed solid is then boiled with 1 N HCl, then the solid is filtered off and washed with water twice to afford the desired product **6a–f** in a 10–48.5% yield.

*4-Chloro-N′-(3-(1-methyl-4-oxo-1,2-dihydroquinazolin-3(4H)-yl)propanoyl)benzohydrazide (**6a**)*
(48% yield). M.p.: 216–219°C. ^{1}H NMR (DMSO-d_6) δ 2.55 (2H, t, *J* 6.8, CH_2CO), 2.83 (3H, s, NCH_3), 3.68 (2H, t, *J* 6.8, NC<u>H</u>$_2$CH$_2$CO), 4.52 (2H, s, NCH_2N), 6.79–6.85 (2H, m, H-6, H-8), 7.40 (1H, t, *J* 8, H-7), 7.57 (2H, d, *J* 8.4, H-3′, H-5′), 7.72 (1H, d, *J* 7.6, H-5), 7.88 (2H, d, *J* 8.4, H-2′, H-6′), 10.06 (1H, s, CO<u>NH</u>NHCOAr exch.), 10.44 (1H, s, CONH<u>NH</u>COAr, exch.). ^{13}C NMR ($CDCl_3$) δ 32.10 (<u>C</u>H$_2$CO), 35.21 (N<u>C</u>H$_3$), 41.62 (N<u>C</u>H$_2$CH$_2$CO), 66.22 (N<u>C</u>H$_2$N), 112.31 (ArCH), 117.14 (ArCH), 118.06 (ArCH), 127.92 (ArCH), 128.57 (ArCH), 129.34 (ArCH), 131.19 (ArC), 133.32 (ArC), 136.62 (ArC), 149.64 (ArC), 162.41 (ArC), 164.45 (ArC), 169.81 (ArC). MS, *m/z*: 385 (M^+), 387 (M^++2). Anal. calcd. for $C_{19}H_{19}ClN_4O_3$: C, 58.99; H, 4.95; N, 14.48. Found: C, 59.26; H, 4.98; N, 14.72.

*4-Chloro-N′-(2-(1-methyl-4-oxo-1,2-dihydroquinazolin-3(4H)-yl)propanoyl)benzohydrazide (**6b**)*
(29.3% yield). M.p.: 96–99°C. ^{1}H NMR ($CDCl_3$) δ 1.51 (3H, d, *J* 7, COCHC<u>H</u>$_3$), 2.95 (3H, s, NCH_3), 4.47 (1H, d, *J* 9.2, NCH_2N), 4.62 (1H, d, *J* 9.2, NCH_2N), 5.44–5.46 (1H, m, CO<u>C</u>HCH$_3$), 6.73 (1H, d, *J* 8, H-8), 6.90 (1H, t, *J* 7.2, H-6), 7.36–7.43 (3H, m, H-3′, H-5′, H-7), 7.73 (2H, d, *J* 8, H-2′, H-6′), 7.95 (1H, d, *J* 7.2, H-5), 8.72 (1H, s, CO<u>NH</u>NHCO, exch.), 9.14 (1H, s, CONH<u>NH</u>CO, exch.). ^{13}C NMR ($CDCl_3$) δ 13.98 (COCH<u>C</u>H$_3$), 36.01 (N<u>C</u>H$_3$), 49.77 (CO<u>C</u>HCH$_3$), 62.84 (N<u>C</u>H$_2$N), 112.47 (ArCH), 117.16 (ArCH), 119.22 (ArCH), 128.82 (ArCH), 128.90 (ArCH), 129.11 (ArCH), 129.94 (ArC), 134.14 (ArC), 138.51 (ArC), 149.76 (ArC), 164.54 (ArC), 165.04 (ArC), 170.46 (ArC). MS, *m/z*: 386 (M^+), 388 (M^++2). Anal. calcd. for $C_{19}H_{19}ClN_4O_3$: C, 58.99; H, 4.95; N, 14.48. Found: C, 59.21; H, 4.99; N, 14.59.

*4-Chloro-N′-(4-(1-methyl-4-oxo-1,2-dihydroquinazolin-3(4H)-yl)butanoyl)benzohydrazide (**6c**)*
(12.28% yield). M.p.: 151–154°C. ^{1}H NMR ($CDCl_3$) δ 1.09 (2H, bs, $COCH_2\underline{CH_2}CH_2$), 2.38 (2H, bs, $\underline{COCH_2}CH_2CH_2$), 2.88 (3H, s, NCH_3), 3.71 (2H, bs, $COCH_2CH_2\underline{CH_2}$), 4.42 (2H, bs, NCH_2N), 6.69 (1H, d, *J* 7.6, H-8), 6.89–6.90 (1H, m, H-6), 7.33–7.39 (3H, m, H-3′, H-5′, H-7), 7.75 (2H, d, *J* 6.8, ArH), 7.93 (1H, d, *J* 6.8, H-5), 9.13 (1H, s, CONHNHCO, exchangeable), 9.91 (1H, s, CONHNHCO, exch.). ^{13}C NMR ($CDCl_3$) δ 24.04 ($COCH_2\underline{C}H_2CH_2$), 31.21 ($CO\underline{C}H_2CH_2CH_2$), 35.90 ($N\underline{C}H_3$), 44.49 ($COCH_2CH_2\underline{C}H_2$), 66.56 ($N\underline{C}H_2N$), 112.13 (ArCH), 117.39 (ArCH), 119.19 (ArCH), 128.76 (ArCH), 128.91 (ArCH), 129.00 (ArCH), 130.04 (ArC), 133.78 (ArC), 138.33 (ArC), 149.28 (ArC), 164.46 (ArC), 164.66 (ArC), 172.06 (ArC). MS, *m/z*: 400 (M^+), 402 (M^++2). Anal. calcd. for $C_{20}H_{21}ClN_4O_3$: C, 59.92; H, 5.28; N, 13.98. Found: C, 59.66; H, 5.25; N, 13.66.

*4-Chloro-N′-(3-(1,2-dimethyl-4-oxo-1,2-dihydroquinazolin-3(4H)-yl)propanoyl)benzohydrazide (**6d**)*
(30.59% yield). M.p.: 107–110°C. ^{1}H NMR ($CDCl_3$) δ 1.16 (3H, d, *J* 5.6, $NCH\underline{CH_3}$), 2.60–2.74 (2H, m, CH_2CO), 2.79 (3H, s, NCH_3), 3.20–3.25 (1H, m, $N\underline{CH_2}CH_2CO$), 4.06 (1H, t, *J* 6.8, $N\underline{CH_2}CH_2CO$), 4.75 (1H, bs, $N\underline{C}HCH_3$), 6.52 (1H, d, *J* 8.4, H-8), 6.75–6.78 (1H, t, *J* 7.2, H-6), 7.27–7.34 (3H, m, H-3′, H-5′, H-7), 7.74–7.81 (3H, m, H-2′, H-6′, H-5), 9.62 (1H, s, CONHNHCOAr), 9.72 (1H, s, CONHNHCOAr). ^{13}C NMR ($CDCl_3$) δ 14.52 ($NCH\underline{C}H_3$), 33.42 ($\underline{C}H_2CO$), 35.33 ($N\underline{C}H_3$), 41.90 ($N\underline{C}H_2CH_2CO$), 73.45 ($N\underline{C}HCH_3$), 112.57 (ArCH), 116.50 (ArCH), 118.28 (ArCH), 128.43 (ArCH), 128.89 (ArCH), 129.10 (ArCH), 130.16 (ArC), 134.07 (ArC), 138.52 (ArC), 146.75 (ArC), 163.13 (ArC), 164.85 (ArC), 170.21 (ArC). MS, *m/z*: 400 (M^+), 402 (M^++2). Anal. calcd. for $C_{20}H_{21}ClN_4O_3$: C, 59.92; H, 5.28; N, 13.98. Found: C, 59.97; H, 5.45; N, 13.85.

*4-Chloro-N′-(4-(1,2-dimethyl-4-oxo-1,2-dihydroquinazolin-3(4H)-yl)butanoyl)benzohydrazide (**6f**)*
(10.6% yield). M.p.: 80–83°C. ^{1}H NMR ($CDCl_3$) δ 1.25 (3H, d, *J* 5.9, $NCH\underline{CH_3}$), 2.01 (2H, bs, $COCH_2\underline{CH_2}CH_2$), 2.37 (2H, t, *J* 6, $\underline{COCH_2}CH_2CH_2$), 2.88 (3H, s, NCH_3), 3.04–3.10 (1H, m, $COCH_2CH_2\underline{CH_2}$), 4.28–4.35 (1H, m, $COCH_2CH_2\underline{CH_2}$), 4.58–4.63 (1H, m, $N\underline{C}HCH_3$), 6.60 (1H, d, *J* 8.4, H-8), 6.85 (1H, t, *J* 7.6, H-6), 7.34–7.40 (3H, m, H-3′, H-5′, H-7), 7.75 (2H, d, *J* 8, H-2′, H-6′), 7.92 (1H, d, *J* 7.6, H-5), 8.97 (1H, s, CONHNHCO), 10.00 (1H, s, CONHNHCO). ^{13}C NMR ($CDCl_3$) δ 13.12 ($NCH\underline{C}H_3$), 23.66 ($COCH_2\underline{C}H_2CH_2$), 30.19 ($CO\underline{C}H_2CH_2CH_2$), 34.46 ($N\underline{C}H_3$), 42.45 ($COCH_2CH_2\underline{C}H_2$), 71.42 ($N\underline{C}HCH_3$), 111.45 (ArCH), 115.75 (ArCH), 117.44 (ArCH), 127.65 (ArCH), 127.90 (ArCH), 129.08 (ArCH), 132.79 (ArC), 132.91 (ArC), 137.27 (ArC), 145.43 (ArC), 162.36 (ArC), 163.61 (ArC), 171.13 (ArC). Anal. calcd. for $C_{21}H_{23}ClN_4O_3$: C, 60.79; H, 5.59; N, 13.50. Found: C, 60.62; H, 5.56; N, 13.36.

Pharmacology

The anticonvulsant activity and neurotoxicity screening were carried out in accordance with the guidelines of the National Research Centre, Dokki, Cairo, Egypt and the whole study was approved by the institutional Medical Research Ethics Committee with a registration number (16064). Adult Swiss albino mice (20–25 g) of both sexes were used as experimental animals and each mouse was used only once. All animals were purchased from National Research Center animal house. The animals were housed at room temperature 22 ± 2°C, under light/dark cycle (12/12) and were allowed free access to food and water. MES and scPTZ are the two animal models used for anticonvulsant activity screening while rotarod test is used for neurotoxicity screening, and the response evaluation was estimated by procedures described elsewhere [31]. The tested compounds were suspended in 1% Tween 80/water mixture and injected intraperitoneally at doses of 30, 100, 300 mg/kg into one to four animals followed by anticonvulsant activity and neurotoxicity assessment at two different time intervals (0.5 and 4 h) after administration.

The MES test
In the MES test, animals were subjected to electrical shock through a current of 60 Hz and 50 mA intensity delivered via ear-lip electrodes for 0.2 s duration. The test compound is considered able to inhibit MES-induced seizure spread upon absence of hind limb tonic extension [28, 32].

The scPTZ test
In the scPTZ test, animals were injected subcutaneously with pentylenetetrazol in a dose of 85 mg/kg at the predetermined time of testing and animals were observed over 30 min. The test compound considered able to abolish pentylenetetrazol induced seizures upon absence of even the threshold seizure (a single episode of clonic spasm of at least a duration of 5 s) [28, 32].

Neurotoxicity-minimal motor impairment (MMI)
Standardized rotarod was the test used to determine the neurotoxicity effect of the tested compounds. Untreated control mouse can maintain its equilibrium when placed on a 6 rpm rotation rod for a prolonged period of time. Acute motor impairment is deduced when the test animal fails to maintain equilibrium on the 6 rpm revolving roller for 1 min in each of three successive trials [28, 32].

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